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CHEMICAL ABSTRACTS, vol. 105, no. 13, September 29, 1986, Columbus, Ohio, USA ; CHANG, RAYMOND S.L., LOTTI, VICTOR J. :"Biochemical and pharmacological characterization of an extremely potent and selective nonpeptide cholecystokinin antagonist", page 51, column 2, abstract-no. 108282u

CHEMICAL ABSTRACTS, vol. 105, no. 13, September 29, 1986, Columbus, Ohio, USA ; EVANS. BEN E., BOCK, MARK G., RITTLE, KENNETH E., DI PARDO ROBERT M., WHITTER, WILLIE L., VEBER, DANIEL F., ANDERSON, PAUL S., FREIDINGER, ROGER M. :"Design of potent, orally effective, nonpeptidal antagonists of the peptide hormone cholexystokinin", page 17, column 2, abstract-no. 107944z

CHEMICAL ABSTRACTS, vol. 106, no. 19, May 11, 1987, Columbus, Ohio, USA ; REIDER, PAUL J., DAVIS, PAUL, HUGHES, DAVID L., GRABOWSKI, EDWARD J.J. :"Crystallization-iduced asymmetric transformation : stereospecific synthesis of a potent peripheral CCK antagonist", page 688, column 2, abstract-no. 156438s

Description

CROSS-REFERENCE

Starting materials for the compounds of Formula I are described in patent application U.S.S.N. 942,131, filed Deceber 16, 1986, which is a CIP of U.S.S.N. 624,853, filed June 26, 1984, now abandoned entitled "Acylaminophenylketones and Amines", which is incorporated herein by reference.

This is a CIP of U.S.S.N. 741,972 filed June 10, 1985, which is a CIP of U.S.S.N. 705,272 filed February 25, 1985, now abandoned, which in turn is a CIP of U.S.S.N. 624,854, filed June 26, 1984, now abandoned.

BACKGROUND OF THE INVENTION

Cholecystokinins (CCK) and gastrin are structurally-related neuropeptides which exist in gastrointestinal tissue and in the the central nervous system (see, V. Mutt, Gastrointestinal Hormones, G. B. J. Glass, Ed., Raven Press, N.Y., p. 169 and G. Nisson, ibid, p. 127).

Cholecystokinins include CCK-33, a neuropeptide of thirty-three amino acids in its originally isolated form (see, Mutt and Jorpes, Biochem. J. 125, 678 (1971)), its carboxylterminal octapeptide, CCK-8 (a naturally-occurring neuropeptide, also, and the minimum fully active sequence), and 39- and 12-amino acid forms, while gastrin occurs in 34-, 17- and 14-amino acid forms, with the minimum active sequence being the C-terminal pentapeptide, Gly-Trp-Met-Asp-Phe-NH_2, which is the common structural element shared by both CCK and gastrin.

CCK's are believed to be physiological satiety hormones, thereby possibly playing an important role in appetite regulation (G. P. Smith, Eating and Its Disorders, A. J. Stunkard and E. Stellar, Eds, Raven Press, New York, 1984, p. 67), as well as also stimulating colonic motility, gall bladder contraction, pancreatic enzyme secretion, and inhibiting gastric emptying. They reportedly co-exist with dopamine in certain mid-brain neurons and thus may also play a role in the functioning of dopaminergic systems in the brain, in addition to serving as neurotransmitters in their own right (see: A. J. Prange et al., "Peptides in the Central Nervous System", Ann. Repts. Med. Chem. 17, 31, 33 [1982] and references cited therein; J. A. Williams, Biomed. Res. 3 107 [1982]); and J. E. Morley, Life Sci. 30, 479, [1982]).

The primary role of gastrin, on the other hand, appears to be stimulation of the secretion of water and electrolytes from the stomach, and, as such, it is involved in control of gastric acid and pepsin secretion. Other physiological effects of gastrin then include increased mucosal blood flow and increased antral motility, with rat studies having shown that gastrin has a positive trophic effect on the gastric mucosa, as evidenced by increased DNA, RNA and protein synthesis.

Antagonists to CCK and to gastrin have been useful for preventing and treating CCK-related and/or gastrin-related disorders of the gastrointestinal (GI) and central nervous (CNS) systems of animals, especially of humans. Just as there is some overlap in the biological activities of CCK and gastrin, antagonists also tend to have affinity for both receptors. In a practical sense, however, there is enough selectivity to the different receptors that greater activity against specific CCK- or gastrin-related disorders can often also be identified.

Selective CCK antagonists are themselves useful in treating CCK-related disorders of the appetite regulatory systems of animals as well as in potentiating and prolonging opiate-mediated analgesia, thus having utility in the treatment of pain [see P. L. Faris et al., Science 226, 1215 (1984)], while selective gastrin antagonists are useful in the modulation of CNS behavior, as a palliative for gastrointestinal neoplasms, and in the treatment and prevention of gastrin-related disorders of the gastrointestinal system in humans and animals, such as peptic ulcers, Zollinger-Ellison syndrome, antral G cell hyperplasia and other conditions in which reduced gastrin activity is of therapeutic value.

Also, since CCK and gastrin also have trophic effects on certain tumors [K. Okyama, Hokkaido J. Med. Sci., 60, 206-216 (1985)], antagonists of CCK and gastrin are useful in treating these tumors [see, R.D. Beauchamp et al., Ann. Surg., 202,303 (1985)].

Four distinct chemical classes of CCK-receptor antagonists have been reported. The first class comprises derivatives of cyclic nucleotides, of which dibutyryl cyclic GMP has been shown to be the most potent by detailed structure-function studies (see, N. Barlos et al., Am. J. Physiol., 242, G 161 (1982) and P. Robberecht et al., Mol., Pharmacol., 17, 268 (1980)).

The second class comprises peptide antagonists which are C-terminal fragments and analogs of CCK, of which both shorter (Boc-Met-Asp-Phe-NH_2, Met-Asp-Phe-NH_2), and longer (Cbz-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-NH_2) C-terminal fragments of CCK can function as CCK antagonists, according to recent structure-function studies (see, R. T. Jensen et al., Biochem. Biophys. Acta., 757, 250 (1983), and M. Spanarkel et al.,

J. Biol. Chem., 258, 6746 (1983)). The latter compound was recently reported to be a partial agonist [see, J. M. Howard et al., Gastroenterology 86(5) Part 2, 1118 (1984)].

Then, the third class of CCK-receptor antagonists comprises the amino acid derivatives: proglumide, a derivative of glutaramic acid, and the N-acyl tryptophans including para-chlorobenzoyl-L-tryptophan (benzotript), [see, W. F. Hahne et al., Proc. Natl. Acad. Sci. U.S.A., 78, 6304 (1981), R. T. Jensen et al., Biochem. Biophys. Acta., 761, 269 (1983)]. All of these compounds, however, are relatively weak antagonists of CCK (IC_{50}: generally 10^{-4}M[although more potent analogs of proglumide have been recently reported in F. Makovec et al., Arzneim-Forsch Drug Res., 35 (II), 1048 (1985) and in German Patent Application DE 3522506A1], but down to 10^{-6}M in the case of peptides), and the peptide CCK-antagonists have substantial stability and absorption problems.

In addition, a fourth class consists of improved CCK-antagonists comprising a nonpeptide of novel structure from fermentation sources [R. S. L. Chang et al., Science, 230, 177-179 (1985)] and 3-substituted benzodiazepines based on this structure [published European Patent Applications 167 919, 167 920 and 169 392, B. E. Evans et al, Proc. Natl. Acad. Sci. U.S.A., 83, p. 4918-4922 (1986) and R.S.L. Chang et al, ibid, p. 4923-4926] have also been reported.

No really effective receptor antagonists of the in vivo effects of gastrin have been reported (J. S. Morley, Gut Pept. Ulcer Proc., Hiroshima Symp. 2nd, 1983, p. 1), and very weak in vitro antagonists, such as proglumide and certain peptides have been described [(J. Martinez, J. Med. Chem. 27, 1597 (1984)]. Recently, however, pseudopeptide analogs of tetragastrin have been reported to be more effective gastrin antagonists than previous agents [J. Martinez et al., J. Med. Chem., 28, 1874-1879 (1985)].

The benzodiazepine (BZD) structure class, which has been widely exploited as therapeutic agents, especially as central nervous system (CNS) drugs, such as anxiolytics, and which exhibits strong binding to "benzodiazepine receptors" in vitro, has not in the past been reported to bind to CCK or gastrin receptors. Benzodiazepines have been shown to antagonize CCK-induced activation of rat hippocampal neurones but this effect is mediated by the benzodiazepine receptor, not the CCK receptor [see J. Bradwejn et al., Nature, 312, 363 (1984)]. Of these reported BZD's, additionally, the large majority do not contain substituents attached to the 3-position of the seven membered ring, as it is well known in the art that 3-substituents result in decreasing anxiolytic activity, especially as these substituents increase in size.

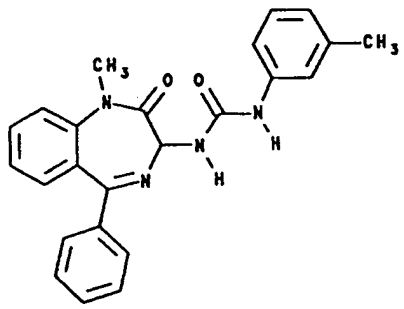
It was, therefore, an object of this invention to identify substances which more effectively antagonize the function of cholecystokinins and gastrin in disease states in animals, preferably mammals, especially in humans. It was another object of this invention to prepare novel compounds which more selectively inhibit cholecystokinins or inhibit gastrin. It was still another object of this invention to develop a method of antagonizing the functions of cholecystokinin and gastrin in disease states in mammals. It is also an object of this invention to develop a method of preventing or treating disorders of the gastrointestinal, central nervous and appetite regulatory systems of mammals, especially of humans, or of increasing food intake of animals.

SUMMARY OF THE INVENTION

It has now been found that the compound of Formula I is an antagonist of gastrin and cholecystokinin (CCK) and binds to the gastrin and CCK receptors. This compound is useful in the treatment and prevention of CCK-related disorders of the gastrointestinal, central nervous and appetite regulatory systems of animals, preferably mammals and especially humans. It is also useful in the treatment and prevention of gastrin related disorders, gastrointestinal ulcers, Zollinger-Ellison syndrome, antral G cell hyperplasia, and other conditions in which reduced gastrin activity is of therapeutic value.

DETAILED DESCRIPTION OF THE INVENTION

The present invention thus provides the compound of formula (I)



and pharmaceutically acceptable salts thereof.

The pharmaceutically acceptable salts of the compound of Formula I include the conventional non-toxic salts or the quarternary ammonium salts of the compound of Formula I formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compound of Formula I by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The ability of the compound of Formula I to antagonize CCK and gastrin makes this compound useful as pharmaceutical agents for mammals, especially for humans, for the treatment and prevention of disorders wherein CCK and/or gastrin may be involved. Examples of such disease states include gastrointestinal disorders, especially such as irritable bowel syndrome, gastroesophageal reflux disease or ulcers, excess pancreatic or gastric secretion, acute pancreatitis, or motility disorders; central nervous system disorders, caused by CCK interactions with dopamine, such as neuroleptic disorders, tardive dyskinesia, Parkinson's disease, psychosis or Gilles de la Tourette Syndrome; disorders of appetite regulatory systems; Zollinger-Ellison syndrome, antral G cell hyperplasia, or pain (potentiation of opiate analgesia); as well as certain tumors of the lower esophagus, stomach, intestines and colon.

The compound of Formula I thereof, may be administered to a human subject either alone or, preferably, in combination with pharmaceutically-acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compound can be administered orally or parenterally, including intravenous, intramuscular, intraperitoneal, subcutaneous and topical administration.

For oral use of an antagonist of CCK, according to this invention, the compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

When a compound according to Formula I is used as an antagonist of CCK or gastrin in a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms. However, in most instances, an effective daily dosage will be in the range of from about 0.05 mg/kg to about 50 mg/kg of body weight, and preferably, of from 0.5 mg/kg to

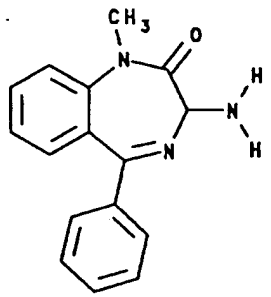
about 20 mg/kg of body weight, administered in single or divided doses. In some cases, however, it may be necessary to use dosages outside these limits.

In the treatment of irritable bowel syndrome, for instance, 0.1 to 10 mg/kg of a CCK antagonist might be administered orally (p.o.), divided into two doses per day (b.i.d.). In treating delayed gastric emptying, the dosage range would probably be the same, although the drug might be administered either intravenously (I.V.) or orally, with the I.V. dose probably tending to be slightly lower due to better availability. Acute pancreatitis might be treated preferentially in an I.V. form, whereas spasm and/or reflex esophageal, chronic pancreatitis, post vagotomy diarrhea, anorexia or pain associated with biliary dyskinesia might indicate p.o. form administration.

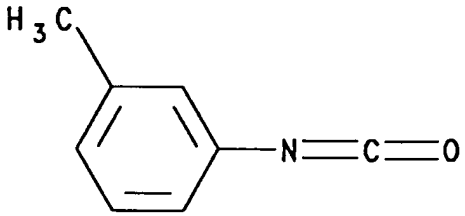
In the use of a gastrin antagonist as a tumor palliative for gastrointestinal neoplasms with gastrin receptors, as a modulator of central nervous system activity, treatment of Zollinger-Ellison syndrome, or in the treatment of peptic ulcer disease, a dosage of 0.1 to 10 mg/kg administered one-to-four times daily might be indicated.

Because this compound antagonizes the function of CCK in animals, it may also be used as feed additives to increase the food intake of animals in daily dosage of approximately 0.05 to 50 mg/kg of body weight.

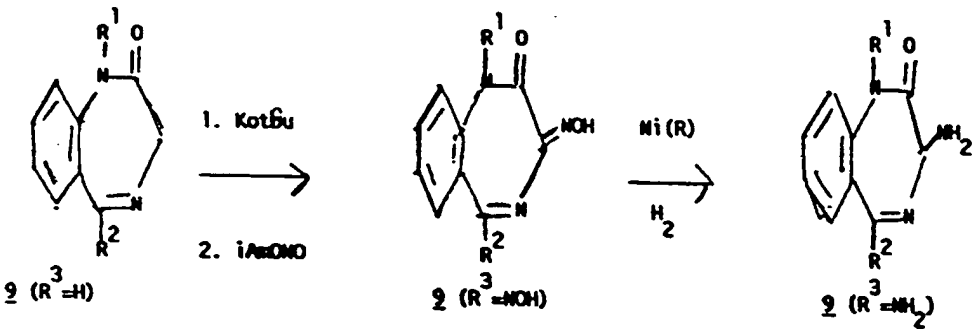
The compounds of Formula I is prepared by reacting an amine of formula



with an isocyanate of formula



SCHEME IVa



(R^2 = phenyl)

3-Amino-5-substituted-1-substituted or unsubstituted benzodiazepines 9 (R^3-NH_2) are prepared as described in the prior art. Alternatively, 9 ($R^3 = NH_2$) are prepared as shown in Scheme IVa. Treatment of the 3-unsubstituted compound 9 ($R^3 = H$) with a suitable base, preferably potassium t-butoxide, followed by a nitrosating agent, preferably isoamyl nitrate, provides the oxime 9 ($R^3 = =NOH$). Reduction, preferably with Raney nickel, gives the 3-amino compounds 9 ($R^3 = NH_2$). Alternatively, 9 ($R^3 = NH_2$) are prepared by the method disclosed in U.S. Patent 4,628,084.

In cases where the starting materials are optically active, the chirality at C_3 is controlled by the synthesis. When racemic starting materials are employed, racemic products are obtained. The enantiomers may be separated by resolution.

In Vitro Activity of Compounds of Formula I

The biological activity of the compounds of Formula I have been evaluated using 1.)an ^{125}I-CCK receptor binding assay and in vitro isolated tissue preparations and 2.) ^{125}I-gastrin and ^{3}H-pentagastrin binding assays.

Materials and Methods

1. CCK Receptor Binding (Pancreas)

CCK-33 was radiolabeled with ^{125}I-Bolton Hunter reagent (2000 Ci/mmole) as described by Sankara et al. (J. Biol. Chem. 254: 9349-9351, 1979). Receptor binding was performed according to Innis and Snyder (Proc. Natl. Acad. Sci. 77: 6917-6921, 1980) with the minor modification of adding the additional protease inhibitors, phenylmethane sulfonyl fluoride and o-phenanthroline. The latter two compounds have no effect on the ^{125}I-CCK receptor binding assay.

Male Sprague-Dawley rats (200-350g) were sacrificed by decapitation. The whole pancreas was dissected free of fat tissue and was homogenized in 20 volumes of ice-cold 50 mM, Tris HCl (pH 7.7 at 25°C) with a Brinkmann Polytron PT 10. The homogenates were centrifuged at 48,000 g for 10 min. Pellets were resuspended in Tris Buffer, centrifuged as above and resuspended in 200 volumes of binding assay buffer (50 mM Tris HCl, pH 7.7 at 25°C, 5 mM dithiothrietol, 0.1 mM bacitracin, 1.2 mM phenylmethane sulfonyl fluoride and 0.5 mM o-phenanthroline). For the binding assay, 25 µl of buffer (for total binding) or unlabeled CCK-8 sulfate to give a final concentration of 1 µM (for nonspecific binding) or the compounds of Formula I (for determination of inhibition of ^{125}I-CCK binding) and 25 µl of ^{125}I-CCK-33 (30,000-40,000 cpm) were added to 450 µl of the membrane suspensions in microfuge tubes. All assays were run in duplicate or triplicate. The reaction mixtures were incubated at 37°C for 30 minutes and centrifuged in a Beckman Microfuge (4 minutes) immediately after adding 1 ml of ice-cold incubation buffer. The supernatant was aspirated and discarded, pellets were counted with a Beckman gamma 5000. For Scatchard analysis (Ann.

N.Y. Acad. Sci. 51: 660, 1949), ^{125}I-CCK-33 was progressively diluted with increasing concentrations of CCK-33.

2. CCK Receptor Binding (Brain)

CCK-33 was radiolabeled and the binding was performed according to the description for the pancreas method with modifications according to Saito et al., J. Neurochem. 37:483-490, 1981.

Male Hartley guinea pigs (300-500g) were sacrificed by decapitation and the brains were removed and placed in ice-cold 50 mM, Tris HCl plus 7.58 g/l Trizma-7.4 (pH 7.4 at 25°C). Cerebral cortex was dissected and used as a receptor source. Each gram of fresh guinea pig brain tissue was homogenized in 10 ml of Tris/Trizma buffer with a Brinkman polytron PT-10. The homogenates were centrifuged at 42,000 g for 15 minutes. Pellets were resuspended in Tris Buffer, centrifuged as above and resuspended in 200 volumes of binding assay buffer (10 mM N-2-hydroxyethyl-piperazine-N'-2-ethane sulfonic acid (HEPES), 5 mM $MgCl_2$, 0.25 mg/ml bacitracin, 1 mM ethylene glycol-bis-(β-aminoethyl-ether-N,N'-tetraacetic acid) (EGTA), and 0.4% bovine serum albumin (BSA)). For the binding assay, 25 µl of buffer (for total binding) or unlabeled CCK-8 sulfate to give a final concentration of 1 µm (for nonspecific binding) or the compounds of Formula I (for determination of inhibition of ^{125}I-CCK binding) and 25 µl of ^{125}I-CCK-33 (30,000-40,000 cpm) were added to 450 µl of the membrane suspensions in microfuge tubes. All assays were run in duplicate or triplicate. The reaction mixtures were incubated at 25°C for 2 hours and centrifuged in a Beckman Microfuge (4 minutes) immediately after adding 1 ml of ice-cold incubation buffer. The supernatant was aspirated and discarded, pellets were counted with a Beckman gamma 5000.

The compounds of Formula I can be determined to be competitive antagonists of CCK according to the following assays.

3. Isolated guinea pig gall bladder

Male Hartley guinea pigs (400-600 g) are sacrificed by decapitation. The whole gall bladder is dissected free from adjacent tissues and cut into two equal halves. The gall bladder strips are suspended along the axis of the bile duct in a 5 ml organ bath under 1 g tension. The organ bath contains a Kreb's bicarbonate solution (NaCl 118 mM, KCl 4.75 mM, CaCl 2.54 mM, KH_2PO_4 1.19 mM, Mg SO_4 1.2 mM, $NaHCO_3$ 25 mM and dextrose 11 mM) maintained at 32°C and bubbled with 95% 0_2 and 5% CO_2. Isometric contractions are recorded using Statham (60 g; 0.12 mm) strain gauges and a Hewlett-Packard (77588) recorder. The tissues are washed every 10 minutes for 1 hour to obtain equilibrium prior to the beginning of the study. CCK-8 is added cumulatively to the baths and EC_{50}'s determined using regression analysis. After washout (every 10 minutes for 1 hour), the compound of Formula I is added at least 5 minutes before the addition of CCk-8 and the EC_{50} of CCK-8 in the presence of the compound of Formula I similarly determined.

4. Isolated longitudinal muscle of guinea pig ileum

Longitudinal muscle strips with attached nerve plexus are prepared as described in Brit. J. Pharmac. 23: ; 356-363, 1964; J. Physiol. 194: 13-33, 1969. Male Hartley guinea pigs are decapitated and the ileum removed (10 cm of the terminal ileum is discarded and the adjacent 20 cm piece used). A piece (10 cm) of the ileum is stretched on a glass pipette. Using a cotton applicator to stroke tangentially away from the mesentery attachment at one end, the longitudinal muscle is separated from the underlying circular muscle. The longitudinal muscle is then tied to a thread and by gently pulling, stripped away from the entire muscle. A piece of approximately 2 cm is suspended in 5 ml organ bath containing Krebs solution and bubbled with 95% O_2 and 5% CO_2 at 37°C under 0.5 g tension. CCK-8 is added cumulatively to the baths and EC_{50} values in the presence and absence of compounds of Formula I determined as described in the gall bladder protocol (above).

Gastrin Antagonism

Gastrin antagonist activity of compounds of Formula I is determined using the following assay.

Gastrin Receptor Binding in Guinea Pig Gastric Glands

Preparation of guinea pig gastric mucosal glands

Guinea pig gastric mucosal glands were prepared by the procedure of Berglingh and Obrink Acta Physiol. Scand. 96: 150 (1976) with a slight modification according to Praissman et al. C. J. Receptor Res. 3: (1983). Gastric mucosa from guinea pigs (300-500 g body weight, male Hartley) were washed thoroughly and minced with fine scissors in standard buffer consisting of the following: 130 mM NaCl, 12 mM $NaHCO_3$, 3 mM NaH_2PO_4, 3 mM Na_2HPO_4, 3 mM K_2HPO_4, 2 mM $MgSO_4$, 1mM $CaCl_2$, 5 mM glucose and 4 mM L-glutamine, 25 mM HEPES at pH 7.4. The minced tissues were washed and then incubated in a 37°C shaker bath for 40 minutes with the buffer containing 0.1% collagenase and 0.1% BSA and bubbled with 95% O_2 and 5% CO_2. The tissues were passed twice through a 5 ml glass syringe to liberate the gastric glands, and then filtered through 200 mesh nylon. The filtered glands were centrifuged at 270 g for 5 minutes and washed twice by resuspension and centrifugation.

Binding studies

The washed guinea pig gastric glands prepared as above were resuspended in 25 ml of standard buffer containing 0.25 mg/ml of bacitracin. For binding studies, to 220 µl of gastric glands in triplicate tubes, 10 µl of buffer (for total binding) or gastrin (1 µM final concentration, for nonspecific binding) or test compound and 10 µl of ^{125}I-gastrin (NEN, 2200 Ci/mmole, 25 pM final) or ^{3}H-pentagastrin (NEN 22 Ci/mmole, 1 nM final) were added. The tubes were aerated with 95% O_2 and 5% CO_2 and capped. The reaction mixtures after incubation at 25°C for 30 minutes were filtered under reduced pressure on glass G/F B filters (Whatman) and immediately washed further with 4 x 4 ml of standard buffer containing 0.1% BSA. The radioactivity on the filters was measured using a Beckman gamma 5500 for ^{125}I-gastrin or liquid scintillation counting for ^{3}H-pentagastrin.

In Vitro Results

1. Effect of The Compounds of Formula I on ^{125}I-CCK-33 receptor binding

Scatchard analysis of specific ^{125}I-CCK-33 receptor binding in the absence and presence of the compounds of Formula I indicated the compound of Formula I competitively inhibited specific ^{125}I-CCK-33 receptor binding since it increased the K_D (dissociation constant) without affecting the B_{max} (maximum receptor number). A K_i value (dissociation constant of inhibitor) of the compounds of Formula I was estimated.

The data of Table 1 were obtained for compounds of Formula I.

TABLE I

CCK Receptor Binding Results			
Compound of Example	IC_{50} (uM)		^{125}I-Gastrin Gastric Glands
	^{125}I-CCK Pancreas	^{125}I-CCK Brain	
1	0.0081	0.0071	0.0031
2	1.4	0.003	0.00066

The most preferred compounds of Formula I are:
N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea, and
(R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea.

In another aspect of the invention is that some of the compounds of Formula I are specific for gastrin as compared to CCK. What is meant by a compound that is "specific" for gastrin is that such compound is at least ten times more potent as an antagonist of gastrin as compared to CCK. Such specificity is highly desirable because a gastrin specific compound can be utilized with essentially no interference with the CCK receptors.

An example of a gastrin specific compound of Formula I is:
(R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea,

The invention is further defined by reference to the following preparations and examples, which are intended to be illustrative and not limiting.

All temperatures are in degrees Celsius.

EXAMPLE 1

N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea

Equimolar amounts of 3(R,S)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 3-methylphenylisocyanate were mixed in 8 ml of dry tetrahydrofuran at room temperature. The reaction mixture was allowed to stand for 8 hours and was then filtered. The collected solids were washed with tetrahydrofuran and dried in vacuo over P_2O_5 to give the analytical product: m.p. 207-209 °C.
NMR: Confirms structure assignment of product
HPLC: Greater than 99% pure.
MS: Molecular ion at m/e = 398.

Anal. Calc'd for $C_{23}H_{22}N_4O_2$:			
	C, 72.34;	H, 5.56;	N, 14.06.
Found:	C, 72.26;	H, 5.22;	N, 14.23.

EXAMPLE 2

(R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea

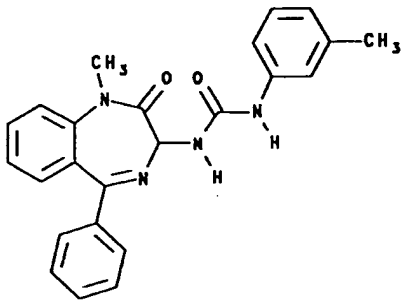
Equimolar amounts of 3(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 3-methylphenylisocyanate were mixed in 8 ml of dry tetrahydrofuran at room temperature. The reaction mixture was allowed to stand for 8 hours and was then filtered. The collected solids were washed with tetrahydrofuran and dried in vacuo over P_2O_5 to give the analytical product: m.p. 208-210 °C.
NMR: Confirms structure assignment of product.
HPLC: Greater than 99% pure.
MS: Molecular ion at m/e = 399 (FAB).

Anal. Calc'd for $C_{24}H_{22}N_4O_2$:			
	C, 72.34;	H, 5.56;	N, 14.06.
Found:	C, 72.12;	H, 5.84;	N, 14.04.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. The compound of formula



and pharmaceutically acceptable salts thereof.

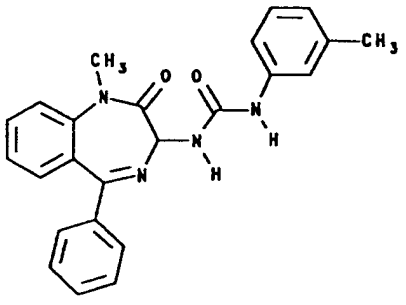
2. A compound as claimed in claim 1 which is (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea.

3. A pharmaceutical composition comprising a compound as claimed in claim 1 or claim 2 and a pharmaceutically acceptable carrier therefor.

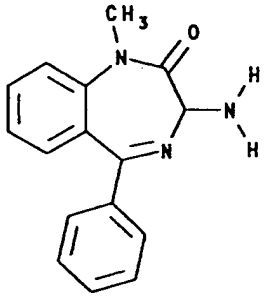
4. The use of a compound as claimed in claim 1 or claim 2 for the manufacture of a mediament for antagonizing the binding of cholecystokinins to cholecystokinin receptors or antagonizing the binding of gastrin to gastrin receptors.

Claims for the following Contracting States : ES, GR

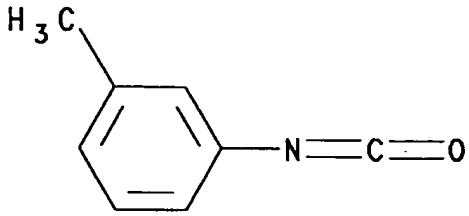
1. A process for the preparation of a compound of formula



which process comprises reacting an amine of formula



with an isocyanate of formula

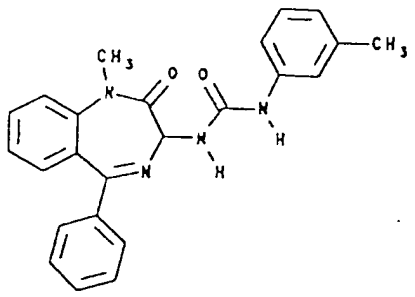


2. A process as claimed in claim 1 for the preparation of (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea.

3. The process as claimed in claim 1 or claim 2 carried out in tetrahydrofuran.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel



und pharmazeutisch verträgliche Salze davon.

2. Verbindung nach Anspruch 1, die (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-harnstoff heißt.

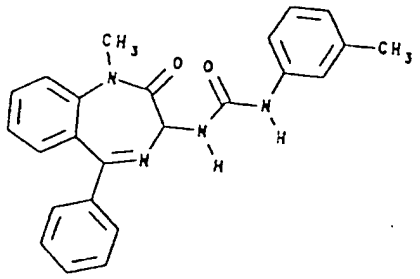
3. Pharmazeutisches Präparat, umfassend eine Verbindung nach Anspruch 1 oder Anspruch 2 und einen pharmazeutisch verträglichen Trägerstoff dafür.

4. Verwendung einer Verbindung nach Anspruch 1 oder Anspruch 2 zur Herstellung eines Medikaments zur Antagonisierung der Bindung von Cholecystokininen an Cholecystokinin-Rezeptoren oder zur

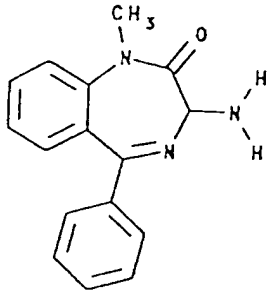
Antagonisierung der Bindung von Gastrin an Gastrin-Rezeptoren.

Patentansprüche für folgende Vertragsstaaten : ES, GR

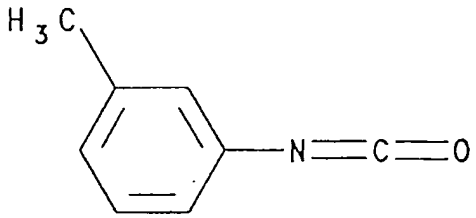
1. Verfahren zur Herstellung einer Verbindung der Formel



wobei das Verfahren die Umsetzung eines Amins der Formel



mit einem Isocyanat der Formel



umfaßt.

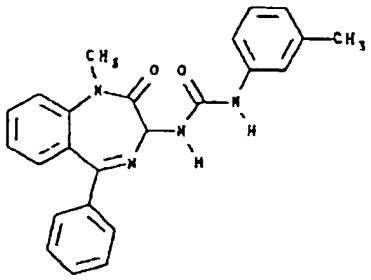
2. Verfahren nach Anspruch 1 zur Herstellung von (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-harnstoff.

3. Verfahren nach Anspruch 1 oder Anspruch 2, das in Tetrahydrofuran durchgeführt wird.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule



et ses sels pharmaceutiquement acceptables.

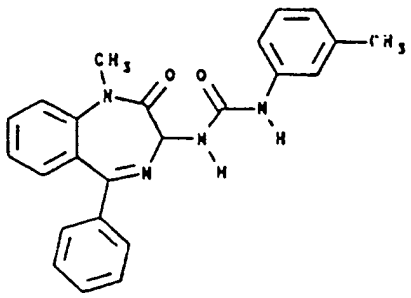
2. Composé selon la revendication 1, qui est la (R)-N-(2,3-dihydro-1-méthyl-2-oxo-5-phényl-1H-1,4-benzodiazépin-3-yl)-N'-(3-méthylphényl)urée.

3. Composition pharmaceutique comprenant un composé selon la revendication 1 ou la revendication 2 et un support pharmaceutiquement acceptable à cet effet.

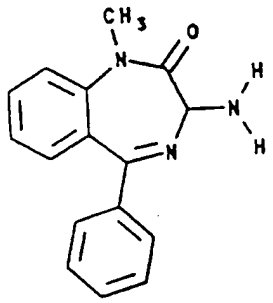
4. Application d'un composé selon la revendication 1 ou la revendication 2 à la préparation d'un médicament pour jouer un rôle d'antagoniste de la liaison des cholécystokinines aux récepteurs de cholécystokinine ou jouer un rôle d'antagoniste de la liaison de la gastrine aux récepteurs de gastrine.

Revendications pour les Etats contractants suivants : ES, GR

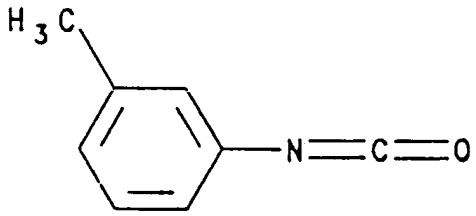
1. Procédé de préparation d'un composé de formule



dans lequel on fait réagir une amine de formule



avec un isocyanate de formule



2. Procédé selon la revendication 1 de préparation de (R)-N-(2,3-dihydro-1-méthyl-2-oxo-5-phényl-1H-1,4-benzodiazépin-3-yl)-N'-(3-méthylphényl)urée.

3. Procédé tel que revendiqué selon la revendication 1 ou la revendication 2 effectué dans du tétrahydrofurane.